

REMARKS

In the Office Action of September 13, 2001, the Examiner objected to the priority claim made to earlier applications under 35 USC §120. Applicants respectfully disagree with this objection for the following reasons.

As provided on page 1, lines 7 through 15 of the specification, this application is a continuation of US Application 09/294,700, issued as US Pat. 6,197,595 on March 6, 2001. This application was filed on December 31, 2000 and was therefore co-pending with US Application 09/294,700. Applicants are also submitting an executed Supplemental Declaration, which also recites all priority applications.

In the office action, the Examiner also rejected claims 90 and 91 under 35 USC §102(b) as anticipated by US Patent 6,130,098 to Handique et al. The Examiner rejected claims 90 and 91 under 35 USC §103(a) as obvious over US Pat. 4,946,795 to Gibbons et al. Applicants respectfully disagree with these rejections.

Based on the priority dates, it is unclear whether the teaching of Handique provided in U.S. patent 6,130,098 is prior art to the present invention. In the following discussion, while the Applicants point out several important patentable differences, they by no means admit that the teaching of Handique in U.S. patent 6,130,098 is prior art.

There are important patentable differences between the claimed invention and the teaching of Handique in U.S. patent 6,130,098. As explained in detail below, Handique does not disclose the claimed microfabricated device having at least first and second chambers disposed therein, wherein at least one of the chambers is a volumetric chamber, and the miniature device is controlled by an external pressure source.

Handique teaches "movement and mixing of microdroplets through microchannels [in] microscale devices, comprising microdroplet transport channels, reaction regions, electrophoresis modules, and radiation detectors. The discrete droplets are differentially heated and propelled through etched channels." (Abstract) While Handique does mention chambers, these are heating or reaction chambers and not volumetric chambers. For example, in col. 3 lines 57-61, Handique discloses: "The present invention contemplates microscale devices, comprising microdroplet transport channels having hydrophilic and hydrophobic regions, reaction chambers, gas-intake

pathways and vents, electrophoresis modules, and detectors, including but not limited to radiation detectors. In some embodiments, the devices further comprise air chambers to internally generate air pressure to split and move microdroplets (i.e. "on-chip" pressure generation)." Furthermore, in col. 4 lines 56-66, Handique discloses: "It has also been found empirically that the methods and devices of the present invention can be used with success when regions of the microchannel are treated with hydrophobic reagents to create hydrophobic regions. By using defined, hydrophobic regions at definite locations in microchannels and using a pressure source, one can split off precise nanoliter volume liquid drops (i.e. microdroplets) and control the motion of those drops through the microchannels."

Perhaps, Handique even teaches away from the claimed invention, in col. 13 lines 63-66, Handique discloses: "The present invention contemplates the use of selective hydrophobic coatings to develop a liquid-sample injection and motion system that **does not require the use of valves.**" On the other hand the volumetric chamber the present invention uses a valve.

When rejecting claims 90 and 91 as anticipated by Handique, the Examiner pointed to the description of Handique related to Figs. 3A and 3B. In col. 14 lines 24-57, Handique discloses:

FIGS. 3A and 3B show a schematic of one embodiment of a device to split a nanoliter-volume liquid sample and move it using external air, said device having a plurality of hydrophobic regions. Looking at FIG. 3A, liquid (shown as a horizontal dashed line) placed at the inlet (20) is drawn in by surface forces and stops in the channel at the liquid-abutting hydrophobic region (40), with overflow handled by an overflow channel and overflow outlet (30). In the embodiment shown in FIG. 3A, the front of the liquid moves by (but does not enter) a gas-intake pathway (50) that is in fluidic communication with the channel; the liquid-abutting hydrophobic region (40) causes the liquid to move to a definite location. Gas from a gas source (e.g. air from an external air source and/or pump) can then be injected (FIG. 3B, lower arrow) to split a microdroplet of length "L". The volume of the microdroplet split-off (60) is predetermined and depends on the length "L" and the channel cross-section. To prevent the pressure of the gas (e.g. air) from acting towards the inlet side, the inlet (20) and overflow ports (30) can be blocked or may be loaded with excess water to increase the resistance to flow.

The patterned surfaces can also be used to control the motion of the drop. By placing a hydrophobic gas vent (70) further down the channel, one can stop the liquid microdroplet (60) after moving beyond the vent (70). As the drop (60)

passes the vent (70), the air will go out through the vent (70) and will not push the drop further.

One can start moving the drop (60) again by blocking the vent (70). By using a combination of hydrophobic air pressure lines (not shown), hydrophobic vents and strategic opening and/or closing of vents, one can move the liquid drop back and forth for mixing or move it to precise locations in a channel network to perform operations such as heating, reaction and/or separations.

In short, Handique uses an access or overflow channel (and not a volumetric chamber) and a hydrophobic region in combination with a vent (not a valve) for measuring a known volume.

On the other hand, the claimed method (or device) is directed to measuring and processing a known volume in a microfabricated device having at least first and second chambers, wherein at least one of the chambers is a volumetric chamber having a known volume. The claimed method (or device) uses at least one valve controlled by an external pressure source. The method includes the acts of filling the volumetric chamber with fluid to create a first aliquot of the fluid; opening the controllable valve; and transporting the first aliquot of the fluid to the at least second chamber by applying pressure from the external source. Therefore, independent claims 90, 93 and 117 are clearly patentable over US Patent 6,130,098 to Handique et al.

In US Patent 4,946,795, Gibbons et al. disclose a device and method that differ significantly from the claimed invention. In col. 2 line 39 through col. 3 line 6, Gibbons discloses:

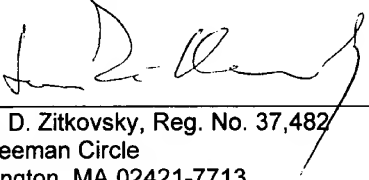
The present invention provides a self-contained dilution apparatus that does not require the use of external force (except unassisted gravity in some cases) to move liquids between its various parts and provide for reproducible dilution of samples. The apparatus comprises a fixed volume measuring chamber; a fixed volume receiving chamber in fluid receiving relationship to the measuring chamber; a gas vent in the receiving chamber; a stop flow junction between the measuring chamber and the receiving chamber; a sample application site in fluid donating relationship to the measuring chamber, wherein the vertical height difference between the sample application site and the stop flow junction is insufficient to provide flow through the stop flow junction when sample is applied to the sample site; and a diluent application site in fluid donating relationship to the measuring chamber. Means for starting flow at the stop flow junction are provided in some cases internally in the apparatus and in other cases are provided by external forces and/or devices. The stop flow junction uses backpressure caused by surface

tension to stop flow of liquid under some circumstances while allowing flow under others. The stop flow junction acts as a valve but has no moving parts, relying on surface tension and the geometry of the junction to accomplish its function. Various means for starting flow include locating the diluent application site sufficiently above the stop flow junction to provide enough hydrostatic pressure to overcome the backpressure at the stop flow junction, including a movable arm or other device proximate to the stop flow junction in order to break surface tension, or providing a vibrator (optionally located externally to the apparatus) to break surface tension. In all cases in which external force is applied as a means for starting flow, this external force is not required for continued flow once flow resumes.

On the other hand, the claimed method (or device) requires external forces for measuring and processing fluid inside the microfabricated device for nucleic acid analysis. To measure and process a known volume of fluid, the microfabricated device includes at least first and second chambers, wherein at least one of the chambers is a volumetric chamber having a known volume, and includes at least one valve controlled by an external pressure source. The claimed method includes the acts of filling the volumetric chamber with fluid to create a first aliquot of the fluid; opening the controllable valve; and transporting the first aliquot of the fluid to the at least second chamber by applying pressure from the external source. Therefore, independent claims 90, 93 and 117 are clearly patentable over US Patent 4,946,795, Gibbons et al. Dependent claims 91, 94 – 116, and 118 – 131 include additional novel combinations of features.

Accordingly, the present application is in condition for allowance and such action is respectfully requested. Please charge all PTO fees and apply all credits to the Deposit Account No. 01-0431.

Respectfully submitted,

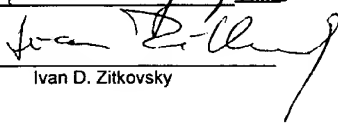

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